Contents

Section 4 – Oral mucositis guidelines

Introduction to Section 4

4.1 Introduction
Overall Goal
Specific Targets and Aims
The Nurse’s Role

Key points to understand from the oral mucositis guidelines

4.2 What is oral mucositis?
Oral mucositis-related symptoms
Grades of oral mucositis

4.3 What are the implications of oral mucositis for the patient?
Consequences of oral mucositis
Impact on chemotherapy dose and cancer outcomes
Quality of life issues
Hospitalisation and related issues

4.4 How is oral mucositis recognised?
Relative risk of developing oral mucositis
Recognising signs of infection

4.5 How is oral mucositis managed?
Radiotherapy – prevention
Standard-dose chemotherapy – prevention
High-dose chemotherapy with or without total-body irradiation
plus haematopoietic stem cell transplantation – prevention
Patient education – oral care
Standard-dose chemotherapy – treatment
Cycles of treatment
Scoring, re-evaluation and monitoring

4.6 How is pain managed in patients with oral mucositis?
Pain assessment
Standardise analgesia treatment

Appendix
Abbreviations
References
4.1 Introduction

Oral mucositis (OM) can be a significant problem for cancer patients, developing as a common side effect of both chemotherapy and radiotherapy. In fact, nearly all patients receiving high-dose chemotherapy with haematopoietic stem cell transplantation (HCST) are affected. OM causes pain and other symptoms that affect quality of life. In addition, OM may become a barrier to successful administration of chemotherapy and/or radiotherapy.

Section 4 introduces the topic of OM and covers the clinical practice guidelines for the prevention and treatment of cancer therapy-induced OM developed by the Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO). These guidelines (written in 2004 and updated in 2005) give recommendations on effective strategies for the prevention and treatment of OM in the setting of radiation therapy, chemotherapy and combined chemoradiation therapy, and also highlight strategies to be avoided in clinical practice.

Overall Goal

Specific Targets and Aims

The Nurse’s Role

4.1.1 Overall Goal

The overall goal of these guidelines is to incorporate the latest developments in OM into standardised patient care.

4.1.2 Specific Targets and Aims

The targets and aims of this module are to:

- Address the differences in mucositis scoring used by clinicians and researchers
- Explain how variations in clinical trial design and implementation have prevented treatment recommendations from being made
- Describe the evolution of patient care (from a variety of clinical practices like oral oncology, radiation oncology, medical oncology and haematology)
- Explain how current OM assessment and management has evolved from clinical experience rather than clinical evidence
- Discuss the evidence to support appropriate OM management

A thorough understanding of the issues in this section should enable:

- Better application of evidence, where it exists, for the prevention and management of patients with OM
- An understanding of the need for appropriate and consistent assessment and scoring of OM
- An understanding, based on current data, of which patients are at high-risk of developing OM
- An understanding of when and where to implement OM guidelines
4.1.3 The Nurse’s Role

Nurses are among the best placed professionals to assess patients for risk by reviewing their patients’ history and current health status. Oncology nurses are in a unique position to recognise, assess and treat the symptoms of OM through their frequent contact with the patients – allowing them to assess risk and intervene with preventive strategies.

There are three key areas where the nurse can make an impact in OM management:\(^3\)
1. Effective assessment and monitoring of the oral cavity and symptoms
2. Disease management and focusing on ensuring appropriate interventions
3. Patient education

These guidelines will highlight the role that nurses play in identifying and managing OM and highlight risk factors associated with it.

Nursing care protocols for OM management may allow more patients to receive chemotherapies on schedule and at full-dose, as well as reducing potential practice variations that could compromise care, promote cost-effectiveness and increase the quality of care for patients.\(^2\) Furthermore, nursing care protocols may help to improve patient quality of life, which is typically affected in OM patients.\(^1\)
4.2 What is oral mucositis?

Oral mucositis (OM) is the inflammation of the mucosal membranes that line the inner surfaces of the mouth. The cells of these linings usually turn over at a rapid rate, which makes them prone to the effects of cancer chemotherapy and radiotherapy.2

The first stage of OM is characterised by injury of the submucosal cells in the mouth. This injury sets off a cascade of events eventually leading to more extensive damage to underlying cells and tissues.2 If OM goes unchecked, cell damage and death can outweigh the cell healing and renewal, thereby shifting the balance towards cell loss. At this point, damage to the mucosa can progress into a more severe ulcerative stage, where the mucosal barrier is broken down. Once it develops, this can put the patient at increased risk for infections of the mouth.2

Oral mucositis-related symptoms

Grades of oral mucositis

4.2.1 Oral mucositis-related symptoms

The inflammation in OM can range from redness, or erythema, to severe ulceration, and is typically associated with pain and discomfort.2 The pain and discomfort can be so severe that it leads to difficulties in eating, drinking, swallowing and speaking extending to an inability to tolerate solid food and liquids, and resulting in impaired nutritional status and inadequate hydration.2

Clinical signs of mucosal damage and cell death may appear after the first 1–2 weeks following radiation therapy, and as early as 3 days after chemotherapy.

The resulting pain and dysfunction of OM can interfere with nutritional intake and result in:3

- Weight loss
- Anorexia
- Malnutrition
- Dehydration

Patients with damaged oral mucosa have an open portal of entry for organisms. In addition, reduced immunity resulting from chemotherapy and radiotherapy makes them prone to opportunistic infections in the mouth, such as:3,4

- Fungal infections (e.g. Candida albicans)
- Herpes infection

OM may also affect the patient’s dental health and gums (e.g. cavities).3
4.2.2 Grades of oral mucositis

The World Health Organisation (WHO) grades OM as follows:\(^5\)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>Grade 0</td>
<td>no changes</td>
</tr>
<tr>
<td>Grade 1</td>
<td>soreness/erythema</td>
</tr>
<tr>
<td>Grade 2</td>
<td>soreness/erythema + ulceration + can eat solid foods</td>
</tr>
<tr>
<td>Grade 3</td>
<td>soreness/erythema + ulceration + can use a liquid diet only</td>
</tr>
<tr>
<td>Grade 4</td>
<td>soreness/erythema + ulceration + oral alimentation is not possible</td>
</tr>
</tbody>
</table>
4.3 What are the implications of oral mucositis for the patient?

Oral mucositis (OM) can be a significant problem for cancer patients (Figure 1). Pain and discomfort can lead to the symptoms mentioned and can have effects on patient quality of life (QoL) and patient outcomes, and lead to increased healthcare costs (e.g. hospitalisation, anti-infective treatment).

**Consequences of oral mucositis**

**Impact on chemotherapy dose and cancer outcomes**

**Quality of life issues**

**Hospitalisation and related issues**

4.3.1 Consequences of oral mucositis

![Diagram](image.png)

**Figure 1: Consequences of OM.**

OM is associated with a high risk of systemic infections and haemorrhage, and can lead to reductions or delays in patients receiving radiotherapy or chemotherapy. OM compromises patient outcomes and leads to increased healthcare costs as a result of prolonged hospitalisation and the need for anti-infective treatment.
4.3.2 Impact on chemotherapy dose and cancer outcomes

Because it is associated with pain, discomfort and a risk of systemic infection, OM is increasingly recognised as a dose-limiting toxicity in cancer therapy. If cancer therapy dose is decreased, it may limit its effectiveness. As a result, OM may be associated an overall worsening of long-term treatment outcomes in cancer. This has led physicians and oncologists to increase awareness of the risks of OM to the medical community. This, in turn, has led to the completion of these OM guidelines.

4.3.3 Quality of life issues

In addition to its local effects, OM has a profound effect on patient well-being and QoL, such as:

- Difficulty chewing and eating
- Loss of taste
- Difficulty drinking
- Difficulty swallowing
- Difficulty speaking
- Abdominal disturbances
- Increased depression
- Sleep disturbances
- Fatigue

These effects further compromise the patients’ response to treatment and/or palliative care. In fact, OM is reported as the most debilitating symptom among transplant patients, as well as those undergoing radiotherapy for head and neck cancer.

4.3.4 Hospitalisation and related issues

Patients suffering from OM may require longer hospitalisation, high doses of analgesics, and intravenous feeding to receive nutrition and maintain hydration. Estimates show that OM can be associated with a mean increase of $35,000 in hospital charges per patient.

4.4 How is oral mucositis recognised?

It is important to recognise oral mucositis (OM) early on, so as to avoid the negative consequences and any negative impact on cancer treatment. In order to do this, one must understand which patients are at the greatest risk and understand how to recognise the signs and symptoms.

Relative risk of developing oral mucositis

Recognising signs of infection

4.4.1 Relative risk of developing oral mucositis

There is a 40% relative risk of developing OM following many standard chemotherapy regimens; but there is a 100% relative risk following high-dose radiotherapy as treatment for head and neck cancers. Furthermore, nearly all patients receiving high-dose chemotherapy with haematopoietic stem cell transplantation (HCST) are affected.

A schematic of the relationship between different therapies and the risk of developing OM is shown in Figure 2. There are varying levels of risk from low to high. The main focus is on grades 2–4 of OM.

![Figure 2: Risk of OM according to type of anticancer treatment.](image)
4.4.2 Recognising signs of infection

Redness and/or ulcerations, ranging from a few millimetres to a few centimetres long can appear on the inner surfaces of the cheeks and lips, the floor of the mouth, the side and bottom surfaces of the tongue, and the soft palate. If ulcerations are noted in these areas, cultures and/or biopsies should be taken from the lesions to rule out viral infections or other causes.4

Other oral manifestations that can be seen in bone marrow recipients and patients undergoing chemotherapy or radiotherapy are:4

- Swelling (edema)
- Superficial infection
- Swollen lymph nodes
- Erythema
- Deep fungal and/or bacterial infections
4.5 How is oral mucositis managed?

Preventing mucositis is preferred to the treatment of its symptoms once it develops. However, until recently, few effective preventive strategies were available. The following section looks at the available therapies, as well as the panel recommendations for each.

Each recommendation has been rated and graded according to standards used in developing guidelines. Please refer to Appendix 1 for an explanation of evidence levels and recommendation grades.

Radiotherapy – prevention

Standard-dose chemotherapy – prevention

High-dose chemotherapy with or without total-body irradiation plus haematopoietic stem cell transplantation – prevention

Patient education – oral care

Standard-dose chemotherapy – treatment

Cycles of treatment

Scoring, re-evaluation and monitoring

4.5.1 Radiotherapy – prevention

The panel provided recommendations on the following therapies for the prevention of oral mucositis (OM) associated with radiotherapy:

- Use of midline radiation blocks and three-dimensional radiation treatment delivery – to reduce mucosal injury (Level II, grade B)
- Benzydamine – for the prevention of radiation-induced mucositis in patients with head and neck cancer receiving moderate-dose radiotherapy (Level I, grade A)
- Sucralfate
- Antimicrobial lozenges
- Chlorhexidine – not to be used to prevent OM in patients with solid tumours of the head and neck who are undergoing radiotherapy (Level II, grade B)
4.5.2 Standard-dose chemotherapy – prevention

The panel provided recommendations on the following therapies for the prevention of OM associated with standard-dose chemotherapy:

<table>
<thead>
<tr>
<th>Recommended</th>
<th>Not recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cryotherapy – 30 minutes of oral cryotherapy in patients receiving bolus 5-fluorouracil (5-FU) chemotherapy (Level II, grade A)²</td>
<td>• Acyclovir – acyclovir and its analogues should not be used routinely to prevent mucositis.² However, it can be considered to prevent other treatment sequelae in the transplant setting, such as herpes simplex virus reactivation (Level II, grade B)²</td>
</tr>
</tbody>
</table>

N.B. The use of cryotherapy is a matter of some debate at the moment. This panel suggests using 20–30 minutes of oral cryotherapy (ice chips) in an attempt to decrease mucositis in patients who are treated with bolus doses of edatrexate.³ Other authors recommend starting 5 minutes before chemotherapy infusion and continuing for 30 minutes⁶.
4.5.3 High-dose chemotherapy with or without total-body irradiation plus haematopoietic stem cell transplantation – prevention

The panel provided recommendations on the following therapies for the prevention of OM associated with high-dose chemotherapy:

**Recommended**

- **Palifermin** – In patients with haematological malignancies receiving high dose chemotherapy and total body irradiation with autologous stem cell transplant, the panel recommends the use of Keratinocyte growth factor-1 (KGF-1; Palifermin [Kepivance™]) at a dose of 60µg/kg/day for 3 days prior to conditioning treatment and for 3 days post-transplant for the prevention of OM.

- **Cryotherapy** – in patients receiving high-dose melphalan in the conditioning phase.

- **Low-level laser therapy** – Low-level laser therapy (LLLT) requires expensive equipment and specialised training. Because of inter-operator variability, clinical trials are difficult to conduct and their results are difficult to compare; nevertheless, the panel is encouraged by the accumulating evidence in support of LLLT. The panel suggests that at centres that are capable of supporting the necessary technology and training, LLLT should be used in an attempt to reduce the incidence of OM and its associated pain in patients who are receiving high-dose chemotherapy or chemoradiotherapy prior to HSCT (Level II, grade B).

**Not recommended**

- **Local granulocyte macrophage colony stimulating factor (GM-CSF) mouthwash** – in the transplant setting with high-dose CT and autologous or allogeneic SCT.

- **Pentoxifylline** – in patients undergoing haematopoietic stem cell transplantation (HSCT) (Level II, grade B).
4.5.4 Patient education – oral care

The panel suggests that oral care protocols which include patient and staff education should be used to attempt to prevent or reduce the severity of OM from chemotherapy or radiation therapy. The panel suggests that protocol development should be interdisciplinary, education should include staff (as well as patients and families), and quality improvement processes should be used to evaluate both protocols and education. The panel suggests that the oral care protocol should include use of a soft toothbrush that is replaced on a regular basis.

Oral care regimens typically include:

- Dental work to eliminate caries and existing gum disease before beginning cancer treatment
- Thorough and frequent cleaning of the oral cavity
- Some form of pain relief, topical anaesthetics or other agents can be considered in established mucositis
- Anti-inflammatory treatment as required
- Aggressive antimicrobial treatment for any new mouth infections

A variety of mouthwashes with mixed actions has been evaluated with positive findings, including:

- Benzydamine hydrochloride
- Corticosteroids
- Chamomile

The following good clinical practices for oral assessment and oral care are also recommended:

- Initial and ongoing assessment using validated instruments, including patient self-report and professional examination
- Preventive oral care regimen
- Therapeutic oral care regimen
- Regular, systematic oral care hygiene with brushing, flossing, bland rinses and moisturisers using a standardised oral care protocol
- Interdisciplinary approach to oral care (nurse, physician, dentist, dental hygienist, dietician, pharmacist and others as relevant)

The following good clinical practices for dental care are also recommended:

- Dental assessment and dental treatment are important before the start of cancer therapy for all patients but especially those with head and neck cancer
- Dental professionals should be members of the interdisciplinary healthcare team throughout active treatment and in follow-up care
4.5.5 Standard-dose chemotherapy – treatment

The panel recommended against the use of the following therapies for the treatment of OM associated with standard-dose chemotherapy:2,15

Chlorhexidine – The panel recommends that chlorhexidine not be used to treat established OM.2

Other treatments may include:

- Antiseptics (povidone iodine, hydrogen peroxide)
- Antibacterial, antifungal and antiviral agents
- Mucosal barriers and coating agents
- Cytoprotectants (beta carotene, vitamin E)

4.5.6 Cycles of treatment

Figure 2 shows the relative risk of developing OM depending on type of anticancer treatment. High-risk patient populations such as high-dose radiotherapy (HDRT) can be identified.6

Approximately 50% patients experiencing mucositis develop recurrent ulcerations and/or oral soreness during subsequent cycles of treatment. The number of treatment cycles strongly correlates with the development of mucositis. Therefore, secondary prophylaxis strategies may be the most appropriate approach for high-risk patients.

4.5.7 Scoring, re-evaluation and monitoring

The exact grading of mucositis is achieved by combining clinical information about pain and nutritional status with oral mucosal reactions. There are a number of scales commonly used: The WHO Oral Toxicity Scale measures anatomical, symptomatic and functional components of OM (see ‘Defining Oral Mucositis’).1 The WHO scale is the most widely known and used because it measures objective, subjective and functional aspects of OM, and it is quick and easy to use.
4.6 How is pain managed in patients with oral mucositis?

Pain and discomfort are common symptoms in oral mucositis (OM). As such, it is important to understand the ways in which pain can be evaluated and dealt with, so as to minimise patient quality of life issues.

**Pain assessment**

**Standardise analgesia treatment**

4.6.1 Pain assessment

Regular oral pain assessment using validated instruments for self-report is essential. A thorough assessment of the patient with OM should include:

- Assessment to determine the source of pain (i.e. due to OM or other reasons)
- Pain assessment to include thorough review of analgesics used, effect and toxicities
- Nutritional assessment
- Quality of life assessment including screening for depression
- Complete oral examination; assessment for local fungal, bacterial or viral infections

4.6.2 Standardise analgesia treatment

**Palliative care (including pain management)** – The panel recommends patient-controlled analgesia (PCA) with morphine as the treatment of choice for OM pain in patients undergoing haematopoietic stem cell transplantation (HSCT). However, the following good clinical practices are also recommended:

- Regular oral pain assessment using validated instruments for self-report is essential
- Topical anaesthetics or other agents can be considered
Appendix 1. Levels of evidence and recommendation grades.

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Type of evidence</th>
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<tbody>
<tr>
<td>I</td>
<td>Evidence obtained from meta-analysis of multiple, well-designed, controlled studies or from high-power randomised, controlled clinical trial</td>
</tr>
<tr>
<td>II</td>
<td>Evidence obtained from at least one well-designed experimental study or low-power randomised, controlled clinical trial</td>
</tr>
<tr>
<td>III</td>
<td>Evidence obtained from well-designed, quasi-experimental studies such as non-randomised, controlled single-group, pre-post, cohort, time or matched case-control series</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence obtained from well-designed, non-experimental studies such as comparative and correlational descriptive and case studies</td>
</tr>
<tr>
<td>V</td>
<td>Evidence obtained from case reports and clinical examples</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Type of supporting evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>There is evidence of type I or consistent findings from multiple studies of type II, III, or IV</td>
</tr>
<tr>
<td>B</td>
<td>There is evidence of type II, III, or IV and findings are generally consistent</td>
</tr>
<tr>
<td>C</td>
<td>There is evidence of type II, III, or IV but findings are inconsistent</td>
</tr>
<tr>
<td>D</td>
<td>There is little or no systematic empirical evidence</td>
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>HDRT</td>
<td>high-dose radiotherapy</td>
</tr>
<tr>
<td>HSCT</td>
<td>haematopoietic stem cell transplantation</td>
</tr>
<tr>
<td>ISOO</td>
<td>International Society of Oral Oncology</td>
</tr>
<tr>
<td>KGF-1</td>
<td>keratinocyte growth factor-1</td>
</tr>
<tr>
<td>LLLT</td>
<td>low-level laser therapy</td>
</tr>
<tr>
<td>MASCC</td>
<td>Multinational Association of Supportive Care in Cancer</td>
</tr>
<tr>
<td>OM</td>
<td>oral mucositis</td>
</tr>
<tr>
<td>PCA</td>
<td>patient-controlled analgesia</td>
</tr>
<tr>
<td>QoL</td>
<td>quality of life</td>
</tr>
<tr>
<td>5-FU</td>
<td>5-fluorouracil</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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References


